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Author manuscript *Proc SPIE Int Soc Opt Eng.* Author manuscript; available in PMC 2020 February 01.

Published in final edited form as: *Proc SPIE Int Soc Opt Eng.* 2019 February ; 10953: . doi:10.1117/12.2515504.

## Quantitative Evaluation of Bone Microstructure using High-Resolution Extremity Cone-Beam CT with a CMOS Detector

S. Subramanian<sup>a</sup>, M. Brehler<sup>a</sup>, Q. Cao<sup>a</sup>, F. J. Quevedo Gonzalez<sup>b</sup>, R. E. Breighner<sup>c</sup>, J. A. Carrino<sup>c</sup>, T. Wright<sup>b</sup>, J. Yorkston<sup>d</sup>, J. H. Siewerdsen<sup>a,e</sup>, W. Zbijewski<sup>a</sup>

<sup>a</sup>Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD USA

<sup>b</sup>Biomechanics Laboratory, Hospital for Special Surgery, New York, NY USA

<sup>c</sup>Department of Radiology and Imaging, Hospital for Special Surgery, New York, NY USA

dCarestream Health, Rochester, NY USA

<sup>e</sup>Russell H. Morgan Department of Radiology, Johns Hopkins University, Baltimore, MD USA

## Abstract

**Purpose:** A high-resolution cone-beam CT (CBCT) system for extremity imaging has been developed using a custom complementary metal-oxide-semiconductor (CMOS) x-ray detector. The system has spatial resolution capability beyond that of recently introduced clinical orthopedic CBCT. We evaluate performance of this new scanner in quantifying trabecular microstructure in subchondral bone of the knee.

**Methods:** The high-resolution scanner uses the same mechanical platform as the commercially available Carestream OnSight 3D extremity CBCT, but replaces the conventional amorphous silicon flat-panel detector (a-Si:H FPD with 0.137 mm pixels and a ~0.7 mm thick scintillator) with a Dalsa Xineos3030 CMOS detector (0.1 mm pixels and a custom 0.4 mm scintillator). The CMOS system demonstrates ~40% improved spatial resolution (FWHM of a ~0.1 mm tungsten wire) and ~4× faster scan time than FPD-based extremity CBCT (FPD-CBCT). To investigate potential benefits of this enhanced spatial resolution in quantitative assessment of bone microstructure, 26 trabecular core samples were obtained from four cadaveric tibias and imaged using FPD-CBCT (75  $\mu$ m voxels), CMOS-CBCT (75  $\mu$ m voxels), and reference micro-CT ( $\mu$ CT, 15  $\mu$ m voxels). CBCT bone segmentations were obtained using local Bernsen's thresholding combined with global histogram-based pre-thresholding;  $\mu$ CT segmentation involved Otsu's method. Measurements of trabecular thickness (Tb.Th), spacing (Tb.Sp), number (Tb.N) and bone volume (BV/TV) were performed in registered regions of interest in the segmented CBCT and  $\mu$ CT reconstructions.

**Results:** CMOS-CBCT achieved noticeably improved delineation of trabecular detail compared to FPD-CBCT. Correlations with reference  $\mu$ CT for metrics of bone microstructure were better for CMOS-CBCT than FPD-CBCT, in particular for Tb.Th (increase in Pearson correlation from 0.84 with FPD-CBCT to 0.96 with CMOS-CBCT) and Tb.Sp (increase from 0.80 to 0.85). This improved quantitative performance of CMOS-CBCT is accompanied by a reduction in scan time, from ~60 sec for a clinical high resolution protocol on FPD-CBCT to ~17 sec for CMOS-CBCT.

**Conclusion:** The CMOS-based extremity CBCT prototype achieves improved performance in quantification of bone microstructure, while retaining other diagnostic capabilities of its FPD-based precursor, including weight-bearing imaging. The new system offers a promising platform for quantitative imaging of skeletal health in osteoporosis and osteoarthritis.

#### Keywords

bone microarchitecture; quantitative imaging; high-resolution; cone-beam CT; CMOS; orthopedic imaging

## 1. INTRODUCTION

Clinical translation of quantitative metrics of trabecular microstructure would benefit from new diagnostic imaging modalities with enhanced spatial resolution. Among potential candidate technologies is cone-beam CT (CBCT) based on amorphous silicon flat panel detectors (a-Si:H FPDs), which offer higher resolution than the detectors used in conventional multi-detector CT (MDCT). CBCT has been proliferating in human maxillofacial and orthopedic applications, including recently introduced extremity CBCT with capability for weight-bearing imaging (Fig. 1 A and Fig. 1 B).<sup>1</sup> We have shown that extremity CBCT can achieve high correlation with reference micro-CT ( $\mu$ CT) in metrics of trabecular microarchitecture (Pearson coefficient of ~0.8–0.9).<sup>2</sup>

To enhance the performance of extremity CBCT in imaging of bone microstructure, we have recently developed a new system by replacing the aSi FPD with a custom CMOS detector.<sup>3,4</sup> The CMOS technology offers higher frame rates, smaller detector pixels, and lower electronic noise than aSi FPD. Furthermore, the thickness of the scintillator used in the prototype CMOS-based scanner was customized to yield optimized detectability of fine details.<sup>3</sup> The resulting CMOS-CBCT achieves ~40% improved spatial resolution in ~4× shorter scan time than FPD-CBCT (17 sec vs. 60 sec.), while maintaining soft-tissue contrast resolution and capability for weight-bearing imaging of the knee and ankle.

A comprehensive study evaluating the performance of CMOS extremity CBCT, FPD extremity CBCT, and MDCT in quantitative evaluation of trabecular architecture in human subchondral bone is ongoing. The study investigates potential benefits of improved spatial resolution provided by CMOS-CBCT in metrics of microstructure and in developing accurate mechanical models of bone. We focus on subchondral bone of the knee because of potential applications in detection of trabecular alterations associated with early osteoarthritis (OA) and in design of joint prostheses. In this paper, we report on comparison of FPD-CBCT and CMOS-CBCT in terms of correlation of metrics of trabecular microarchitecture against gold-standard micro-CT.

#### 1.1 Sample preparation and experimental workflow.

Four human cadaver tibias were obtained through an anatomical donations program. Intact tibias were scanned using MDCT, FPD-CBCT and CMOS-CBCT. Based on the MDCT scans, a bone-specific drilling and cutting guide was 3D printed for each tibia to allow precise removal of proximal articular surfaces and accurate positioning of bone cores. With

the help of the guide, the tibial plateau was removed using an oscillating saw and 5–8 coring kerfs of ~8 mm diameter were drilled in the exposed trabecular bone of each specimen, leaving distal attachment of the core intact. Before the cores were extracted from the tibias, another set of MDCT scans was obtained. The post-coring scans (combined with the use of bone-specific drill guides) will enable accurate localization of the cores in CBCT and MDCT volumes of intact tibias through simple rigid registration. In this manner, we will be able to compare computed local tissue strains derived from quantitative CBCT/MDCT-based finite-element models of complete proximal tibias to those computed from models based on scans of only the cores obtained on micro-CT.

After the final MDCT scans, the tibias were cut distally perpendicular to the tibial shaft at  $\sim$ 32 mm from the exposed proximal surface to extract the cores. In total, 26 samples were obtained. All cores were imaged in a single acquisition on MDCT, FPD-CBCT and CMOS-CBCT using the configuration illustrated in Fig. 1. A  $\sim$ 50 mm diameter water cylinder with bone mineral density (BMD) calibration inserts at 75 mg/mL CaHA and 150 mg/mL CaHA was placed in the field of view together with the samples. The cores were then imaged individually on a micro-CT system. Here, we will compare metrics of trabecular microarchitecture obtained from CBCT scans of the cores to those measured in gold-standard  $\mu$ CT.

#### 1.2 CBCT scanners and imaging protocols.

Both the FPD-CBCT and CMOS-CBCT were developed using the mechanical platform of Carestream OnSight3D extremity CBCT. The gantry design provides the unique capability for weight-bearing imaging of the lower extremity in natural standing stance (Fig. 1 A). To enable such acquisitions, the source and detector are mounted on a sickle-shaped arm that permits the detector to slide between the patients' legs during the scan. The height and angulation of the gantry can be adjusted, providing the capability for imaging of unloaded upper and lower extremities in addition to weight-bearing scanning (Fig. 1 B). The experiments described here were performed with FPD-CBCT and CMOS-CBCT in the configuration for weight-bearing imaging of the knee and the samples positioned in the center of the field-of-view.

Key differences between the two CBCT systems involve: (i) a 0.5 focal spot stationary anode three-source x-ray tube on FPD-CBCT compared to a 0.3 focal spot single-source rotating anode x-ray tube (IMD RTM 37) on CMOS-CBCT; and (ii) a Varex PaxScan2530 aSi FPD with pixel size of 0.137 mm and a 0.7 mm CsI scintillator on FPD-CBCT compared to a Dalsa Xineos3030 CMOS detector with 0.099 mm pixels and a custom 0.4 mm thick CsI on CMOS-CBCT. The imaging protocols involved 90 kVp beam energy and a 210° short scan trajectory with detectors operated at their native pixel size. Scan times were ~60 sec on FPD-CBCT and 17 sec on CMOS-CBCT (owing to the faster readout of the CMOS). The FPD-CBCT and CMOS-CBCT datasets were reconstructed with Feldkamp filteredbackprojection algorithm using a Hann apodization filter with cutoff at 0.7 Nyquist frequency of each detector. Voxel size was 75  $\mu$ m. All CBCT reconstructions were converted to BMD units using the calibration phantom. The reference  $\mu$ CT was obtained on a Scanco Medical MicroCT 35 unit. The  $\mu$ CT voxels measured 15  $\mu$ m.

## 1.3 Image analysis and metrics of bone microarchitecture.

To enable structural analysis, the  $\mu$ CT and CBCT volumes were processed to generate binary bone segmentations. We followed our previously developed framework for robust trabecular measurements in CBCT.<sup>2</sup> First, regions of interests (ROIs) were identified in the  $\mu$ CT of each core. Binary ROI masks were mapped to the CBCT volumes using transformations obtained from rigid registration of  $\mu$ CT and CBCT reconstructions. Note that the measurements were performed on the original reconstructed datasets and only the masks were geometrically transformed to ensure that the same ROI was evaluated in each modality.

Segmentations of  $\mu$ CT scans were obtained using Otsu's method. For CMOS-CBCT and FPD-CBCT, we applied a two stage approach involving global pre-thresholding followed by local Bernsen's segmentation.<sup>5</sup> In the pre-thresholding step, a Gaussian curve was fit to the global image histogram and all voxels with values below that corresponding to 50% of maximum of the fit were set to zero.<sup>2</sup> Bernsen's segmentation assigned each voxel to bone or background depending on mid-grey value of a sliding window centered on that voxel.<sup>5</sup>

Bernsen's segmentation algorithm has two free parameters, the radius of the sliding window and the local contrast threshold. A parameter sweep across a range of radius and contrast threshold was performed to identify optimal combination of parameters for each modality. Standard sphere-fitting methods<sup>6</sup> were used to obtain the following structural measurements from the segmented CBCT volumes: trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp), trabecular number (Tb.N) and bone volume over total volume (BV/TV).

## 2. RESULTS AND BREAKTHROUGH WORK

Fig. 2 compares axial µCT and CBCT slices through three example bone cores. (The images were rigidly registered for display.) The cores are representative of the range of trabecular thicknesses present in the study sample. The higher spatial resolution of CMOS-CBCT leads to noticeably less blurring of the trabeculae. The 3rd and 4th column of Fig. 2 shows the results of global pre-thresholding (grayscale background image) and subsequent local thresholding (red overlay) of CMOS-CBCT and FBP-CBCT volumes. CMOS-CBCT yields thinner and better delineated trabecular segmentations.

Measurements of bone microstructure obtained with FPD-CBCT and CMOS-CBCT are compared to reference  $\mu$ CT in Fig. 3. Each data point represents mean metric value in the measurement ROI for one sample. CMOS-CBCT achieves better correlation with  $\mu$ CT for all metrics. Consistent with reduced blurring of the trabeculae observed in Fig. 2, the most pronounced improvement was in Tb.Th, where Pearson correlation coefficient increased from 0.84 with FPD-CBCT to 0.96 with CMOS-CBCT. For all metrics, the spread of measured values around the trendline was reduced with CMOS-CBCT.

Fig. 4 further illustrates the improved measurement of Tb.Sp and Tb.Th with CMOS-CBCT. Rigidly registered axial maps of local Tb.Sp and Tb.Th are compared for the three modalities. CMOS-CBCT achieves better agreement with µCT for both metrics. Because of the small size of the trabeculae compared to the intertrabecular spacing, the effects of the improved spatial resolution of CMOS-CBCT are particularly pronounced for Tb.Th Local

values of Tb.Th are lower in CMOS-CBCT than in FPD-CBCT and the regions of non-zero thickness along each trabeculae are thinner, resulting in a map that is more consistent with reference µCT.

#### CONCLUSIONS 3.

The prototype extremity CBCT based on a custom-optimized CMOS sensor achieves enhanced performance in quantitative evaluation of bone microstructure compared to the FPD-based system. Consistent with increased spatial resolution of CMOS-CBCT, the most notable improvement was found in estimation of Tb.Th, where the prototype system obtained ~15% better correlation with  $\mu$ CT.

The high-resolution CMOS-based system maintains the diagnostic capabilities of currentgeneration FPD extremity CBCT, including soft-tissue visualization and weight-bearing imaging. By combining those capabilities with enhanced performance in quantification of bone microstructure, CMOS-CBCT provides a compelling platform for development of novel biomarkers of osteoporosis and osteoarthritis, where current imaging modalities lack the spatial resolution to probe microstructural changes caused by the disease.

## ACKNOWLEDGEMENTS

Work supported by NIH grants R01-EB-018896, R21-CA-208821, and collaboration with the Carestream Health (Rochester NY).

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## Figure 1.

(A) Extremity CBCT in configuration for weight-bearing imaging. (B) Extremity CBCT in configuration for unloaded imaging of the lower and upper extremities. (C)Axial slice of a CMOS-CBCT scan of tibial bone cores. All cores were imaged in a single acquisition together with a BMD calibration phantom. In this work, we compare metrics of trabecular microstructure derived from CMOS-CBCT and FPD-CBCT of the cores against gold-standard micro-CT.



## Figure 2.

Axial slices through three example trabecular bone cores are compared for  $\mu$ CT (left column), FPD-based extremity CBCT (2<sup>nd</sup> column) and the prototype CMOS-based CBCT (3<sup>rd</sup> column). Improved spatial resolution of CMOS-CBCT results in better delineation of trabecular detail. The 4<sup>th</sup> and 5<sup>th</sup> column show segmentations obtained with FPD- and CMOS-CBCT. The grayscale background image is the result of global pre-thresholding. Red contours delineate the final segmentation obtained with local Bernsen's thresholding of the pre-thresholded volume.



## Figure 3.

Comparison of metrics of trabecular microarchitecture derived from FPD-CBCT (top row) and CMOS-CBCT (bottom row) to reference micro-CT. Pearson correlation coefficients are reported in top left corner of each graph. Identity line denoted in blue. CMOS-based system achieves improved correlation across all metrics, in particular for Tb.Th (~15% increased correlation coefficient).



#### Figure 4.

Rigidly registered maps of local Tb.Sp and Tb.Th for three of the core samples. CMOS-CBCT yields local estimates of Tb.Sp and Tb.Th that are more consistent with reference  $\mu$ CT than FPD-CBCT.